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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,481	03/07/2006	Masahiko Kuroda	2006 0025A	7350

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EXAMINER	
SALMON, KATHERINE D	

ART UNIT	PAPER NUMBER
1634	

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10/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,481	KURODA ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10 and 11* is/are pending in the application.

4a) Of the above claim(s) *2-5,10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/31/2009 has been entered. It is noted that the claim set examined is the claim set from 2/27/2009.

2. Claims 1-8 and 10-11 are pending. Claim 9 has been cancelled.

3. Claims 2-5 and 10-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/20/2007 and made FINAL.

4. This action for claims 1 and 6-8 is NonFINAL. Response to arguments is provided after the rejection.

Claim Rejections - 35 USC § 112/2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-8 are indefinite because the claim does not recite a clear nexus between the preamble of the claim and the process steps of the claims. The preambles state a method for diagnosing endometriosis. The positive active steps of the claims are drawn to detection of the expression level of HRF and the degree of endometriosis or risk of endometriosis. The claim is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are steps of diagnosis of endometriosis. Because these steps are missing there is no positive active step to diagnosis.

Claim Rejections - 35 USC § 112/ Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for A method for determining increased risk of endometriosis in a human, said method comprising measuring an expression level of histamine releasing factor (HRF) polynucleotide in a menstrual blood sample from a human subject, detecting a higher expression level of the HRF polynucleotide from the subject as compared to a normal biological sample, wherein a higher expression level of the HRF polynucleotide from the subject is indicative of a subject having an increased risk of endometriosis does not reasonably provide enablement for the diagnosis of a human for endometriosis or determining the degree of endometriosis. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The breadth of the claims and nature of the invention

Claim 1 is drawn to a method for diagnosing endometriosis in a human comprising measuring an expression level of HRF polynucleotide in a menstrual blood sample from a human and comparing the expression level with that in a normal biological sample wherein a subject exhibiting a higher HRF expression level is indicative of a subject having endometriosis or a subject at risk thereof. Claim 6 is drawn to a method for diagnosing endometriosis in a human comprising preparing RNA from a menstrual blood sample of a human and comprising the signal level of a labeled HRF probe to an index of HRF expression level wherein using higher HRF polynucleotide expression level when compared to a normal biological sample indicates the degree of endometriosis or risk thereof. Claim 7 is drawn to a method for diagnosing endometriosis in a human comprising preparing RNA from menstrual blood

and measuring the expression level wherein higher HRF expression level compared to a normal biological sample indicates the degree of endometriosis or risk thereof. Claim 8 is drawn to a method for diagnosing endometriosis comprising preparing RNA from the menstrual blood of a human wherein a higher expression level compared to a normal biological sample reflects the degree of endometriosis or risk thereof.

The nature of the invention not only involves determining the expression level of the HRF polynucleotide, but correlation of the expression level to the diagnosis of endometriosis or the correlation of the expression level to the degree of endometriosis.

Guidance in the Specification and Working Examples

The specification asserts that HRF polynucleotide expression level in a biological sample, such as, menstrual blood can be used as an index to diagnose the endometriosis related disease (p. 12 lines 25-30). However, the instant specification provides no data for the association of menstrual blood expression levels and diagnosis of endometriosis.

The specification provides an example of expression levels of HRF with other biological samples. As discussed below these expression levels were not predictably associated with diagnosis of endometriosis. Further, as discussed below the different biological sample types examined in the working examples disclosed different correlations in expression. Therefore, the working examples disclose that dependent on the biological sample used, the expression level is different. As such, even if, a correlation was obtained in the data provided in the instant specification this data would not be directly correlative to expression in menstrual blood.

The specification teaches collecting tissue samples from 18 patients. The specification teaches that the samples were endometriosis implants, eutopic endometrium from endometrial patients and normal endometrial tissues from patients having no endometriosis (pg 24, lines 25-30). The specification and figure 1 teach that only 3 out of 5 endometriosis patients exhibited higher HRF expression levels in the implant tissue as compared to the normal tissue (pg 28, lines 3-6). Also, figure 2 demonstrates the results from northern blot analysis of HRF expression (pg 28, lines 21-26). Figures 2A and 2B teach that the expression levels for the eutopic endometrial samples and the normal samples had approximately the same expression levels, and that only some of the endometrial implants exhibited higher expression levels as compared with the normal. Since there is no significant demonstrated increase in HRF expression levels between endometrial tissue (both eutopic and implant) samples and normal tissue samples, the data indicates that is it unpredictable to use HRF expression levels from endometrial tissue as a means of determining the presence of endometriosis.

The unpredictability of the art, the state of the prior art, level of skill in the art

The applicant has provided data in the 37 CFR 1.132 declaration by Masahiko Kuroda (filed 8/31/2009). Masahiko Kuroda provides data which measures expression levels of HRF gene in menstrual blood from normal subjects and endometriosis patients (p. 3 1st paragraph). The 1.132 discloses that cDNA was synthesized from menstrual blood from 7 normal patients and 30 endometriosis patients (p. 3 2nd paragraph). The 1.132 asserts that figure A shows the results of real time PCR wherein expression

levels of HRG gene in menstrual blood from endometriosis patients were much higher than that from normal patients (p. 4 last paragraph).

Figure A of the 37 CFR 1.132 discloses the expression levels of HRF cDNA in menstrual samples from endometriosis patients and normal subjects and the statistical correlation with a student's t-test and a Welch's t-test (p. 5). These tests both provide a statistically significant pvalue (p. 5). Masahiko Kurado asserts that diagnosis of endometriosis is possible by measuring expression levels of HRF gene in menstrual blood (p. 6 1st paragraph). Masahiko Kurado asserts that the claimed invention is therefore enabled for diagnosing endometriosis by measuring expression levels of HRF in menstrual blood (p. 6 1st paragraph).

However, although the 37 CFR 1.132 submitted provides data confirming the increased risk of endometriosis in a human by detection of increased expression levels of HRF in menstrual blood, it does not provide data for the correlation of increased expression levels to the diagnosis of endometriosis or degree of endometriosis. The data presented by the 37 1.132 does not disclose any data towards a diagnosis of endometriosis in a patient that has not been previously identified as having endometriosis. As shown by Pepe et al, discussed below, there must be a very large odds ratio to show a predictable correlation of diagnosis. Herein in the instant case, although the data discloses that patients with endometriosis have higher expression of HRF, the data does not provide that patients which do not have endometriosis can be clinically evaluated for a future occurrence of endometriosis. Further, neither the instant specification nor the 37. 1.132 provide any evidence that the expression of HRF is

correlative to a particular degree of endometriosis. As such, the data presented in the instant application is correlative to an increased risk of endometriosis, but not towards a correlation to diagnosis or degree of endometriosis.

Pepe et al. (American Journal of Epidemiology 2004 Vol. 159 p. 882) teaches that for a marker associated with a disease to be effective for classifying persons according to their current or future outcome, that the odds ratio must be of a magnitude rarely seen in epidemiological studies (abstract). Figure 2 of Pepe et al. shows the probability distribution of a maker and shows that the OR scores must be at least 25 to actually show differences between the normal and the disease populations (Figure 2). Therefore in the instant case the specification has not provided a predictable correlation of diagnosis of a patient for endometriosis.

The art teaches genetic expression associations are often irreproducible. Shalon (Shalon et al. US 2001/0051344 A1 Dec 13, 2001) teaches that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph 0155). Shalon further teaches that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph 0156). Shalon teaches that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least

2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to control levels for the same gene (see page 10, paragraph 0158). Therefore the art teaches that genetic differences in individuals affect the expression levels of genes and make it difficult to provide a clear association between expression and disease. Although the 37 1.132 presents a study in which 30 patients with endometriosis has higher levels of HRF expression as compared to normal patients, the data is not directly correlative to a future determination of a patient who does not have endometriosis (e.g. diagnosis). As shown both by Pepe et al. and Shalon, such a correlation to diagnosis must be reevaluated in a large population with a large odds ratio to be clinically predictive.

Quantity of Experimentation and Conclusion

Claims 1 and 6-8 are broadly drawn to diagnosis or degree of endometriosis. The specification does not provide any working examples of such a correlation. As shown both by Pepe et al. and Shalon, such a correlation to diagnosis must be reevaluated in a large population with a large odds ratio to be clinically predictive. Further, the 37 CFR 1.132 submitted discloses data which provides support for a correlation of increased risk, however, the data does not provide any example of a patient without endometriosis being diagnosed with endometriosis before the actual disease occurrence.

Therefore the method as claimed would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that

art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments and *Affidavit or Declaration under 37 CFR 1.132*

The reply traverses a 35 USC 112 Enablement rejection. The arguments set forth in the reply are summarized below with response to arguments following.

The reply asserts that the declaration provided by the invention provides a statistical analysis showing that endometriosis can be diagnosed by measuring the expression level of HRF (p. 2 2nd paprahgra-3rd paragraph). The reply asserts that in particular the degree of reliability based on the data given in Figure A is 95% (p. 2 2nd paragraph).

The Declaration under 37 CFR 1.132 filed 8/31/2009 is not sufficient to overcome the 35 USC 112/Scope of Enablement presented above.

The applicant has provided data in the 37 CFR 1.132 declaration by Masahiko Kuroda (filed 8/31/2009). Masahiko Kuroda provides data which measures expression levels of HRF gene in menstrual blood from normal subjects and endometriosis patients (p. 3 1st paragraph). The 1.132 discloses that cDNA was synthesized from menstrual blood from 7 normal patients and 30 endometriosis patients (p. 3 2nd paragraph). The 1.132 asserts that figure A shows the results of real time PCR wherein expression

levels of HRG gene in menstrual blood from endometriosis patients were much higher than that from normal patients (p. 4 last paragraph).

Figure A of the 37 CFR 1.132 discloses the expression levels of HRF cDNA in menstrual samples from endometriosis patients and normal subjects and the statistical correlation with a student's t-test and a Welch's t-test (p. 5). These tests both provide a statistically significant pvalue (p. 5). Masahiko Kurado asserts that diagnosis of endometriosis is possible by measuring expression levels of HRF gene in menstrual blood (p. 6 1st paragraph). Masahiko Kurado asserts that the claimed invention is therefore enabled for diagnosing endometriosis by measuring expression levels of HRF in menstrual blood (p. 6 1st paragraph).

The data in the 37 CFR 1.132 and the arguments in the reply have been fully reviewed but have not been found persuasive.

However, although the 37 CFR 1.132 submitted provides data confirming the increased risk of endometriosis in a human by detection of increased expression levels of HRF in menstrual blood, it does not provide data for the correlation of increased expression levels to the diagnosis of endometriosis or degree of endometriosis. The data presented by the 37 1.132 does not disclose any data towards a diagnosis of endometriosis in a patient that has not been previously identified as having endometriosis. As shown by Pepe et al, discussed below, there must be a very large odds ratio to show a predictable correlation of diagnosis. Herein in the instant case, although the data discloses that patients with endometriosis have higher expression of HRF, the data does not provide that patients which do not have endometriosis can be

clinically evaluated for a future occurrence of endometriosis. Further, neither the instant specification nor the 37. 1.132 provide any evidence that the expression of HRF is correlative to a particular degree of endometriosis. As such, the data presented in the instant application is correlative to an increased risk of endometriosis, but not towards a correlation to diagnosis or degree of endometriosis.

Pepe et al. (American Journal of Epidemiology 2004 Vol. 159 p. 882) teaches that for a marker associated with a disease to be effective for classifying persons according to their current or future outcome, that the odds ratio must be of a magnitude rarely seen in epidemiological studies (abstract). Figure 2 of Pepe et al. shows the probability distribution of a maker and shows that the OR scores must be at least 25 to actually show differences between the normal and the disease populations (Figure 2). Therefore in the instant case the specification has not provided a predictable correlation of diagnosis of a patient for endometriosis.

Conclusion

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

/Sarae Bausch/
Primary Examiner, Art Unit 1634